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PERSPECTIVES

Human Challenge Studies With Wild-Type Severe Acute Respiratory Sydrome Coronavirus 2 Violate Longstanding Codes of Human Subjects Research

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This manuscript explores the ethics of human inoculation experiments in young healthy adults with wild-type severe acute respiratory sydrome coronavirus 2 (SARS-CoV-2) as a tool to evaluate vaccine efficacy in the context of the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report, and in the context of dose-response relationships with infectious agents. Despite societal pressure to develop a SARS-CoV-2 challenge model to evaluate vaccines, we argue that there are substantial risks that cannot be adequately defined because the dose of SARS-CoV-2 that causes severe disease in young adults is unknown. In the absence of curative therapy, even if a volunteer consents, longstanding ethical codes governing human subjects research preclude the conduct of such experiments.

Keywords. ethics; human challenge experiments; SARS-CoV-2; vaccines.

We are writing to discuss the ethics of human challenge experiments with severe acute respiratory sydrome coronavirus 2 (SARS-CoV-2) as a tool to accelerate vaccine licensure. This approach involves randomizing healthy volunteers (18 to 25 years old) to vaccine or placebo and then infecting all volunteers with SARS-CoV-2 to assess vaccine efficacy [1–3]. The justifications for the development of this model in young healthy adults are that the risks for morbidity and mortality in this age group are negligible, participants have a right to accept such risks "free from paternalistic overreach," and there is a "societal value of reducing the time required to identify efficacious vaccines against a disease that is creating a massive and relentless daily toll" [1, 4, 5]. Concerns expressed in opposition to this approach have centered around its utilitarian morality, the possible adverse short-term and long-term health outcomes—including death—in the volunteers, the inability to manage risks associated with experimental infection, the adequacy of informed consent, the time required to develop a model, the utility of a model in accelerating vaccine development, and the reduction in confidence in the research community should adverse events occur [6–8].

We recently published a letter voicing some of these concerns [8]. Shortly thereafter, we were invited to participate in a debate with advocates of the human challenge experiments, including 1Day Sooner, an organization that has signed up over 38 000 volunteers from 166 countries to participate in SARS-CoV-2 challenge trials, which have entered the planning stage in the United Kingdom but have yet to receive regulatory approval [9]. 1Day Sooner has received significant coverage, much of it positive, in the news media, including but not limited to stories in *National Geographic*, the *New York Post*, and CNBC [10–12]. In preparation for the debate, which was sponsored by the Rikers Debate Project and the Central Synagogue of Manhattan and can be viewed at https://youtu.be/v1XpQK8nkFg, we realized that although there had been a great deal written concerning the ethics of such experiments [2, 3, 13, 14], there had been little direct discussion of whether human challenges with SARS-CoV-2 are compatible with longstanding ethical codes of human subjects research.

There are 3 documents that have long guided human subjects research: the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. The overarching theme of these documents is that as physicians and scientists, we are obligated to protect individuals from experiments that might benefit society but harm an individual.

The Nuremberg Code, written in 1947 in response to experimentation done on prisoners in concentration camps in World War II, states that "no experiment

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should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except perhaps in those experiments where the experimental physicians also serve as subjects" [15]. The Declaration of Helsinki, first published in 1964 and primarily directed to physicians, rejects even that exception [16]. The Declaration states that physicians should only engage in research that safeguards the health of participants; the goal of new knowledge "can never take precedence over the rights and interests of individual research subjects" and that "the responsibility for the protection of research subjects *must always rest with the physician and never with the research subjects, even though they have given consent.*" The Declaration goes on to state that "physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately addressed and can be successfully managed." Finally, the Belmont Report, published in 1979 in response to the Tuskegee syphilis study, includes the concept of Beneficence: do no harm and maximize possible benefits [17]. For healthy people who are experimentally infected with SARS-CoV-2 or any other infectious agent, there is potential harm and no benefit. Because there is no benefit, the ethical standard for human inoculation experiments is that the disease must be entirely self-limited or there must be a curative therapy [13, 18], which currently does not exist for SARS-CoV-2.

Those who have advocated for SARS-CoV-2 challenges have stated that the risks of morbidity and mortality in young healthy persons are negligible, based on extrapolated infection rates, and therefore such infections are permissible [1]. Those in opposition have stated that the risks of severe illness, death, protracted symptoms, and postinfectious complications such as thromboembolic events, prolonged pulmonary, cardiac, or renal dysfunction and cognitive impairment are substantial, based on the outcomes of young adults who tested positive for SARS-CoV-2 [8, 19]. For example, 2.5% of those aged 20–29 years old who were diagnosed with SARS-CoV-2 in Indiana have been sick enough to be hospitalized. However, as is discussed below, the severity of illness for many infectious agents is dose dependent. Thus, the truth of the matter is that no one can define the risks of SARS-CoV-2 human challenges because we do not know the dose of SARS-CoV-2 that causes severe infection in young healthy persons.

If we have learned anything from human infection experiments, for several pathogens outcome is clearly dose dependent. For example, in our *Haemophilus ducreyi* skin infection model, volunteers develop infection (papules) at almost all inoculated sites in the 1–150 colony-forming unit (CFU) dose range; in 30% of the volunteers, all papules spontaneously resolve, whereas abscesses form in 70% of the volunteers [20]. This host effect is reproducible when the volunteers are challenged a second time [21]. For doses >150 CFUs, the host effect on outcome is lost in that abscesses develop at all sites; for doses >1000 CFUs, abscesses form too rapidly to mimic natural infection [20, 22]. In some models, the infectious dose is strain dependent; for example, there is 100-fold difference in the median infective dose (ID_{50}) of 2 gonococcal strains used to infect male volunteers [23]. For the initial human trials done with coronavirus 229-E in 1967, the infectious dose that caused common colds in 66% of the volunteers was only $10^{1.2}$ to $10^{1.5}$ 50% tissue culture infectious dose ($TCID_{50}$). Some have advocated that initial dose-ranging experiments for SARS-CoV-2 challenges should include doses of 1×10^2, 1×10^3, and 1×10^4 $TCID_{50}$ [2, 3], which are 3 logs lower than the doses used in recent influenza challenge models [24, 25]. However, if SARS-CoV-2 operates in a very low and narrow dose range similar to coronavirus 229-E, we may not be able to easily distinguish between doses that lead to asymptomatic or mild infection versus those that cause severe disease and death in young healthy volunteers.

CONCLUSIONS

The emerging data from phase III trials showing the high efficacy of the Pfizer, Moderna, and AstraZeneca vaccines in the prevention of disease due to SARS-CoV-2 lessen the argument for the development of a SARS-CoV-2 challenge model. However, proponents have stated that a challenge model may be needed to evaluate next-generation vaccines in the setting of low levels of circulating virus [2]. Nevertheless, we conclude that the risks of a wild-type SARS-CoV-2 human challenge model cannot be defined but are potentially substantial, and, at this time, severe disease cannot be adequately managed. Although to some it may seem paternalistic, according to our ethical codes, in the absence of curative therapy, even if a volunteer consents, sponsors, physicians, and scientists are bound to refuse to conduct such trials.

The SARS-CoV-2 pandemic has led to tremendous pressure to develop therapeutics and vaccines, which has resulted in premature acceptance of therapies, such as hydroxychloroquine, that proved to be toxic or not beneficial, because we did not follow longstanding rules of scientific rigor [26]. Similarly, the pandemic should not lead us to ignore or revise our longstanding codes of ethics regarding human subjects research.

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